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OFFICIAL PUBLICATION OF THE AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE

VOLUME 1
JULY 1961
NUMBER 2

AMERICAN ASSOCIATION
FOR THE STUDY OF
HEADACHE

Annual Meeting

NEW YORK

PARK SHERATON HOTEL

JUNE 25, 1961

9:00 A.M. to 12:00 Noon
1:00 P.M. to 5:00 P.M.

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. . . Editorial . . .

The original plans of the American Association for the Study of Headache call for the publication "Headache" in January, April, July and October. However, due to the fact that our annual meeting is held just preceding the A.M.A. meeting, the Editorial Office thought it would be advisable to have this copy in your hands just prior to our meeting.

Our official program will be found under the section, "Organizational News," in this issue. We hope that you will be able to join us in the Park-Sheraton Room of the Park-Sheraton Hotel in New York, June 25. Our program should be of interest to you physicians who find headache as a frequent complaint in your medical practice.

Daily we find membership steadily growing. An application blank may be found in this issue for those desiring membership in this organization.

"Headache" is in its infancy and there are many problems which we have had to overcome. We hope that you, our readers, have enjoyed these first two issues and we welcome your suggestions or comments.

HEADACHE

Official Publication of the American Association for the Study of Headache

VOLUME I JULY, 1961 NUMBER 2

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Table of Contents

PAGE

EDITORIAL 1

PENTERGOT INSERTS 5
ROBERT E. RYAN, M.D., M.S., B.S.

MUSCLE RELAXATION IN THE TREATMENT OF HEADACHE 8
LESTER S. BLUMENTHAL, M.D., AND MARVIN FUCHS, M.D.

SOME IMPORTANT FEATURES OF MIGRAINE 22
WALTER C. ALVAREZ, M.D.

PAIN IN THE ANTERIOR PORTION OF THE TEMPLES 26
HENRY D. OGDEN, M.D.

THE ROLE OF PLACEBO RESPONSE IN CLINICAL HEADACHE EVALUATIONS 31
GUNTHER H. FREY, M.D.

OFFICIAL PROGRAM FOR THE MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE 39

ABSTRACTS 41

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PENTERGOT INSERTS

For the Symptomatic Treatment of Migraine

ROBERT E. RYAN, M.D., M.S., B.S.
St. Louis University, St. Louis, Mo.

ONE OF THE most common complaints encountered by the practicing physician today is headache. Headache is in itself not a disease but is a symptom of a disease or illness which may be either organic or functional. Because of the fact that so many different types exist, headache constitutes an enormous clinical problem in the field of medicine today.

The most important phase of the handling of any chronic headache problem is the establishment of a correct diagnosis. This, in my opinion, is obviously true in the handling of any medical problem, because without the diagnosis, the proper type of treatment cannot be given to the patient. Therefore, each headache problem must be classified. In classifying headache there are many factors which have to be established and known by the physician.

Probably the most important simple factor in enabling a physician to establish a correct diagnosis of any headache problem is the taking of a thorough case history. This is especially true when one is dealing with a vascular headache problem. This is due to the fact that there are no definite findings in the physical examination. In order to obtain a complete history the physician has to help the patient.

Taking a case history from patients having chronic headache may often be a long, rather involved process, and may require more than one interview. The use of leading questions simplifies this task and ensures a correct diagnosis. However, it must be stated that the patient himself has a responsibility to answer all of the questions of the physician truthfully. This can often be a factor in the misdiagnosis of a headache problem when the patient fails to tell his story accurately.

Diagnosis of the types of headache a patient has should not be attempted until the patient has completely described his symptoms and until the results of his general physical examination, laboratory test, and special diagnostic procedures have been reviewed.

The physician must remember that many problems of chronic headache may occur independently of the existence of any specific disease, while others may occur as a constant symptom of a particular disease. The problem of differential diagnosis of a headache problem can definitely be a complicated one.

The field of headache therapy has had its sufficient share of investigative research during the past score of years. This is especially true when the field of vascular headache is considered. Various preparations which have the ergot derivatives as their basis have proven to be of considerable benefit when dealing with the symptomatic phase of headache treatment.

It must be remembered by both the physician and the patient that there is no short cut when they deal with the treat-

ment of a chronic headache. The patient should also remember that most of the preparations which are on the open drug market are usually utterly useless if they are used without the advice of a competent physician.

The objective of all headache treatment should be to alleviate the pain and to prevent subsequent attacks.

The symptomatic treatment of migraine has, in the last several years, been a wide, speculative field. There have been so many preparations initially presented in the medical literature as being successful that it would be impossible to name them all.

The symptomatic form of treatment should be directed towards alleviating the pain of the headache attack.

During the last few years, several new preparations have been used in the symptomatic treatment of migraine.

It should be pointed out that in the past decade there has been an abundance of papers in the medical literature which deal with a symptomatic form of treatment of migraine. Each of these papers points out to the medical profession that at last there is a "cure all" for the migraine patient. The odd thing about most of these preparations is that an article appears which describes excellent results with a drug and then usually nothing is further reported on the subject. These preparations have no doubt been used by many, but failing to produce the desired results, they are discarded and nothing is written or said about them again. The literature is full of accounts of drugs which are said to cure certain percentages of migraine cases. However, when these preparations are actually applied to the migraine patient, they do not seem to work as well as one would generally expect them to after reading the first enthusiastic reports. In many migraine cases, the physician is often desperate to produce relief for his patient. For this reason, both he and the patient are willing to try anything.

I have been using a suppository which is made up of 2 mg. of Ergotamine, 100 mg. of caffeine, 60 mg. of pentobarbital and .250 mg. of Hyoscyamine sulfate. This preparation is called Pentergot insert. Hyoscyamine sulfate is a para-sympathetic inhibitor and has no effect on the relief from the headache attack at all, but is used merely to combat any gastric side effects which might occur. The Ergotamine tartrate acts as a sympathetic sedative and caffeine as a central stimulant. Of course, the pentobarbital is used for its sedative effect. The results obtained with this preparation are shown in Table No. 1.

The Pentergot insert produces little or no gastric side effects, as is found with the oral ergotamine preparations. However, this preparation did produce side effects in the form of a sleepy sensation to various degrees.

Ergotamine sometimes causes nausea and vomiting. Since many patients have nausea with their headaches, it is difficult at times to determine whether the illness or the medicine is responsible.

TABLE NO. 1

RESULTS OBTAINED

	No. of Cases	—Results— Excellent	Good	Poor	Gastric Side Effects
Pentergot Insert	200	172 (86%)	16 (8%)	12 (6%)	4 (2%)

Excellent = complete relief.
Good = partial relief.
Poor = no relief.

Many migraine patients experience so much nausea and vomiting with attacks that it is practically an impossibility for them to retain any type of medication taken orally. This, plus the fact that absorption through the stomach is poor following nausea and vomiting, has led to the idea of the rectal suppository form of administration.

In many cases it was rather confusing to the patient when he was told to take a preparation rectally for the purpose of relieving his headache attack. It should be explained to the patient that this suppository will in no way act as a laxative but is merely intended to help relieve the headache attack. It should be explained further that the suppository should be taken as soon as possible after the headache attack starts. One suppository seems to be the best average dosage.

The migraine headache patient has long been looking for something to give them relief from their attacks. Pentergot inserts seem to be the answer to their problem. But, it should be remembered by both the patient and the physician, that these suppositories are for the symptomatic form of treatment only and their headache problem, to be treated completely satisfactorily, must be attacked both prophylactically and symptomatically. The physician will find Pentergot inserts solve the symptomatic phase of the problem, but his patient also wants something which will prevent future attacks, and the manufacturers of this new preparation make no claim in this respect whatsoever.

Unless both phases of headache therapy are given to the patient, he will not get the results which he is seeking. The average patient having a headache has tried various preparations which are advertised to be a "cure-all" for all forms of headache before he consults the physician for advice.

The objectives of all headache therapy should include the alteration of the pain mechanism which is taking place.

The psychologic reaction which is taking place and which is causing the patient's headache attacks is stimulated by something. It is this stimulus which the physician has to identify and isolate. Once he finds this, he must explain it to the patient and advise him how he may avoid it. If this stimulus cannot be avoided completely by the patient, he must be shown by the physician how he may adjust himself so as to minimize its effects. This may be done in some cases by merely enabling the patient to obtain a better understanding of his own abilities and his own limitations.

Pentergot inserts are not a "cure-all" which will give 100 per cent results in all cases of migraine; no preparation will ever fit into this category. However, the results obtained by the use of this preparation are extremely encouraging, and it is definitely a drug of choice when treating this type of patient.

Muscle Relaxation in the Treatment of Headache

By

LESTER S. BLUMENTHAL, M.D.

and

MARVIN FUCHS, M.D.

Washington, D.C.

HEADACHE is a complex phenomenon. We often forget that the headache patient is an integrated, functioning human being. His complicated background and life situation form the basis and actually a nest in which the headache attacks develop. Whether the headache is predominantly vascular, as seen in migraine and Horton's headache, or predominantly tension, the chain of events leading to the attack is similar. Whenever these patients become tired, anxious, tense or upset from emotional and physical strain, they are more likely to develop a headache. Much has been written about the anxious, tense type of personality, who leaves himself vulnerable for attacks of migraine or tension headache.[1,2,3] Certain occupations place a patient in such a position as to produce physical spasm and tension of the muscular elements about the head and neck. The telephone operator is the most frequent example of this seen in our practice.

The automobile is proving to be of prime etiologic importance in the production of headache. Acute cervical strains, produced by sudden thrust of the head in a to-and-fro motion upon the shoulders, upon impact of a moving vehicle (so-called "whiplash injury") is often followed by a typical symptom complex. Sudden abnormal flexion, extention and rotation of the head upon the neck stretches and often tears ligamentous and muscular structures, decreasing the normal support and protection afforded the underlying tissues. This in turn allows for stretching and contusions of the nerve roots and blood vessels in the cervical area. Let us take the trouble to re-examine the anatomy of the cervical vertebrae, the course of the nerve roots, the carotid and vertebral arteries and their branches, the origins and insertions of the muscles and ligaments that attach to the base of the skull and to each surface, spinous process and articular facet of the cervical vertebrae.[4] We will soon realize that these **acute** cervical strains can thrust and propel the head and neck **beyond their normal range** of motion **only** by overstretching or tearing the supporting structures. The damaged tissues soon become adematous and tender, resulting in secondary spasm of the surrounding adjacent supporting structures. This is nature's way to attempt to limit further strain to the damaged muscles and adjacent tissues.

In evaluating a patient with headache, it is more important to understand the pathophysiology involved than it is to make a pigeonhole diagonsis. As we talk to our patients, we can soon determine how much emotional or physical tension

is involved. Even the classic migraine that responds to ergot usually presents a rigid, tense appearance, and actually feels the muscular structures of the back of the head and neck becomes tense and spastic.

Evaluation, Diagnosis and Setting the Stage for Therapy

In our evaluation of the patient with headache[5] every effort is made to take a complete and detailed history, allowing the patient ample time (often at several visits) to ventilate his description of his pain and also anything else he might have on his mind that he wishes to talk about. In this way, we soon get a general picture of the type of individual the patient happens to be. In return, the patient gets a feeling that we are indeed interested in him as a person, and not just another case number. This alone acts to reassure the patient and to give him confidence in the physician. The resultant relief of anxiety is followed by a noticeable relaxation and lowering of tension. The physical examination, X-ray and laboratory study that follows the history, serves to assure the patient that we are leaving no stone unturned in our effort to determine all factors that might be relevant to his condition.[6] Once our examinations are concluded, a lengthy and detailed discussion of all factors with the patient, and any interested relative or friend, is the true cornerstone for successful treatment. The patient must be reassured that there is no "brain tumor," that he does not have a "broken neck," that his headaches will not lead to a "stroke" or "blood clot," and yes, don't forget to reassure the patient that his headaches are not a sign that he is "going crazy." The patient will not come out and ask you these things, but after suffering at length with headaches, these doubts crop up into his mind time and again. Your frontal overall approach and reassurance of all of these factors will do as much as any medication to relieve his anxieties. I dwell so much on this explanation of all factors to the patient because indeed it is not only just an explanation, but it is a major part of the treatment itself. By means of this, you again reassure the patient, you get his undivided attention and co-operation. He is then "tuned in" to each direction and prescription you offer him.[7] It is then, and only then, that physical therapy, vasodilating drugs, vasoconstrictors,[8] sedation, analgesia,[3] tranquilization,[9] cerebral enzymes and their inhibitors,[10] and muscle relaxation[11] can be properly prescribed.

Skeletal Muscle Spasm

Muscle spasm can be the primary cause of head pain in our telephone operators, or in a salesman driving for miles with the window open and getting a stiff neck. More often muscle spasm is secondary to some other condition, such as acute cervical strain,[12] cervical arthritis,[13] discogenic disease of the cervical spine,[14] occipital neuralgia[15] or, as part and parcel of a migraine or tension headache attack.

It is only recently that agents have been available for relaxation or prevention of muscle spasm. This can be brought about by action on the muscles themselves, on the myoneural junction, or by central action on the brain or brain stem. One of the first such preparations was Mephenesin (myanesin).[16] Meprobamate was first used clinically for its muscle relaxant effect.[17] Its tranquilizing properties were later recognized and proved to be its most important clinical indication.[18] Zoxazolamine (Flexin),[19] chlormethazanone (Trancopal),[20,21] chlorzoxazone (Paraflex) and carisoprodol (Soma)[11,22] are some of the muscle relaxant preparations now in clinical use.

Orphenadrine hydrochloride (Disipal) has been used in the treatment of Parkinson's syndrome (paralysis agitans) since 1955.[23] It soon became apparent that the agent effectively relieved muscle spasm in a wide variety of skeletal muscle and neurologic disorders.[24] In order to provide long-term relaxation of skeletal muscle spasm, the citrate salt of orphenadrine (Norflex) has been incorporated in a plasticized matrix. The active ingredi-

ent leaches from this plasticized matrix in a cumulative manner—45 per cent in the first hour, 65 per cent by the fourth hour and is completely released within twelve hours. This preparation therefore eliminates the crest and trough effect encountered with shorter-acting preparations.

Pharmacology of Orphenadrine Citrate

The pharmacologic action and toxicity of the citrate salt was found to be identical to that of the hydrochloride (Disipal).[25] Significant side effects have not been reported from this slowly released form of orphenadrine. In a "Triple blind" study involving 400 subjects, 100 of whom received placebo, 300 of whom received Norflex, the incidence of side actions in each of the two groups was low, and not significantly different. Those that did occur were typical of parasympatholitic drugs: dryness of the mouth and blurring of the vision. Some older persons reported excess stimulation, confusion and a sense of unreality. Occasional incidence of nausea and/or vomiting was reported. Reduction of the daily dosage eliminated the side effects in virtually every case.

The clinical action of the drug involves neither a blocking of the myoneural junction nor actions at the cord level. The central nervous system action at higher levels appears to be involved. There are polysynaptic reflex pathways for pain in skeletal muscle contraction. Afferents may reach the thalamus by way of the lateral spinothalmic tract. A thalamocortical radiation exists for pain appreciation with inter-connections in the motor cortex. Muscle spasms may, as in Parkinsonism, result from impingement at the mid-brain level on upper motor neurons. Thus, orphenadrine relaxes skeletal muscle which is in spasm, but does not reduce the general tonus of skeletal muscles. This relative degree of specificity, no doubt, accounts for the fact that there was no significant difference in side effects between the placebo group and the group receiving orphenadrine in the study cited above. The apparent result is that muscles which do not require relaxation are not affected with either salt.[26]

Material and Methods

We have used orphenadrine citrate in our headache clinic and private medical practice since October, 1959. To date, 220 patients have been treated, 125 of these patients had various types of head and neck pain, 95 patients had various joint or muscle painful or spastic disorders, ranging from backache, bursitis of the shoulder, chest wall pain to carcinoma with pain. These conditions will be briefly summarized and discussed at the end of the paper. Our main purpose in this study was to evaluate the effect of muscle relaxation in the major headache categories.

Each patient included in this study received a thorough history, physical and laboratory analysis before institution of therapy. Most of these patients have lived with their headache problems long enough to be able to evaluate their response to therapy and to compare the action of one drug with another. Proper evaluation of any drug is impossible without accurate classification of the headache on a physiologic basis. In each case we attempt to make our diagnosis based upon the actual physiologic changes that are predominant in that particular patient. The 125 patients included in this study were accordingly classified into the following four groups:

1. **VASCULAR —** Included in this group are several different entities.
   - A. Typical and atypical "histaminic cephalalgia." This entity has been described periodically throughout the years as "Sluder's" neuralgia, "cluster" headache, "Horton's" headache, "atypical face pain" and a "new variety of headache."
   - B. Migraine in its classical, typical and atypical forms.
   - C. Other vascular headaches that present a heavy, full, congested feeling in the head, with or without scotomata, photophobia, nausea and vomiting.
   - D. Hypertension headache is usually classified as a vascular headache.

Many of our vascular headache patients have hypertension and many did not. In our opinion hypertension is but an accompanying condition to the headache which presents itself in the same way, whether there is hypertension present or not.

E. Temporal arteritis is also usually included as a vascular headache but no cases were included in this study.

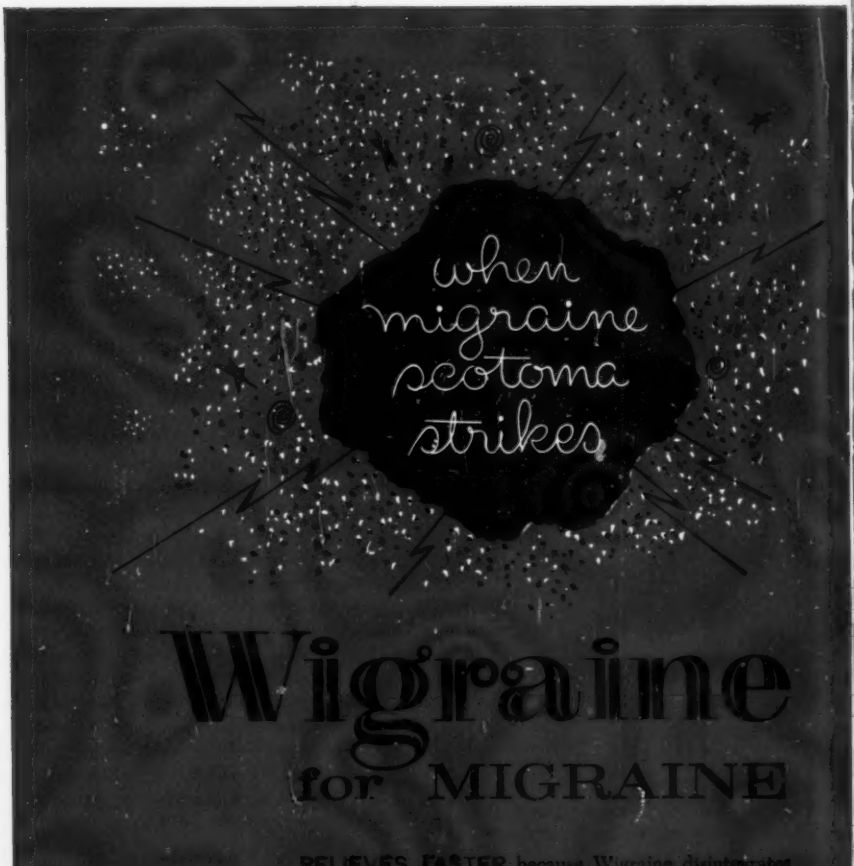
2. **TENSION HEADACHE** — Irritation and spasm of the muscular elements at the back of the head and neck can produce muscle tension headache. The same tissues can go into spasm from any heightened emotional condition such as anxiety, apprehension, fatigue, fear, guilt, resentment or frustration. With careful questioning and observation, we were able to determine that those included in this group actually initiated their attacks with tension features. It is true that many of these patients will develop vascular features and at times actually a true migraine picture if **the heightened emotional or physical tension is allowed to continue.** These vascular features are in our opinion secondary to the basic tension features. At this stage of the attack ergotamine preparations will usually relieve the vascular features without affecting the basic tension elements.

3. **ARTHRITIS OF THE CERVICAL SPINE** — Most of us will develop some degree of arthritis of the cervical spine as we age. We see many healthy patients without an ache or a pain or a complaint of any kind, whose X-ray of the cervical spine presents the appearance of severe degenerative arthritis. Many of them also show marked narrowing of the intervertebral spaces and complete destruction of the intervertebral discs without symptoms of any kind. All patients included in this category in our series had definite evidence of arthritis of the cervical spine with severe head and neck symptoms. Because of the lack of symptoms in other patients with similar X-ray findings and because of the nature of their complaints, it is our opinion that most such cases actually have their headache based upon tension of the muscular and ligamentous structures about the head and neck, rather than the arthritic changes. The results found from the results shown in the group of patients were so similar to that found in typical tension headache that this makes the relation even more obvious. Most authors do not separate these groups, and apparently list them all as tension headaches.

4. **POST-TRAUMATIC HEADACHE**— We include in this group a patient whose head or neck pain begins with, or is markedly exacerbated by, an accident. Other popular names for this syndrome are "acute cervical strain," "whiplash lesion," and "post-concussion syndrome." Each patient included in this group had a definite accident. The most common form was an automobile collision in which the patient, usually a passenger in one of the cars, had his head thrust violently to and fro upon his neck at the time of impact. No patient included in this series had any significant headache problem before the accident.

The dominant features of this syndrome include an accident followed by generalized shaking up and nervous condition for several days with the actual headache developing after an interval of time. The patient then complains of severe, recurrent headaches, usually at the back of the neck and the top of the head, vertigo, inability to focus his eyes, a cloudy, thick, full, congested feeling in the head or a feeling of not being able to think clearly. Nausea and vomiting are often present for a short period of time after the accident. Many such individuals have actual radiation of pain into the neck, shoulder, chest, or

(Continued on Page Thirteen)



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Muscle Relaxation

(Continued From Page Eleven)

arm. Some will have typical radicular type pain, apparently due to compression of nerve roots. When such a series of events continues, and painful attacks are allowed to go on, there often is, as described above under tension headache, a secondary vascular element, which may have many features of migraine, but here again careful history and evaluation will determine that the trauma to the muscular and ligamentous tissues are at fault.

DOSAGE:

Treatment periods varied from five days to seventeen months. At times orphenadrine citrate was the only medication prescribed. It was often, however, added to other therapeutic regimens or medications. At the beginning of our study, the data available to us included references to possible gastrointestinal upsets, dizziness, confusion, restlessness and insomnia. In looking back at the cases treated early in this series, we can readily see that iatrogenic factors were frequently and inadvertently projected into the prescription of orphenadrine. We would often tell a patient that "the drug might keep you awake at night, so therefore don't take it after 5:00 p.m." or "it might upset your stomach, so if it does, let me know." But we soon realized that we were projecting these ideas and fears into the patient's reaction. Since January 1, 1960, we therefore advised the average patient to take one tablet each morning and one each afternoon. Those patients weighing 120 pounds or less were started with one-half tablet twice a day. An occasional patient misunderstood our directions and took as many as three or four tablets a day. As it turned out, this was an extra dividend, because we then learned that the benefits were occasionally heightened by repeated doses throughout the day.

Each patient was seen at frequent intervals at which time complete notes were made as to the action of the drug and any unpleasant reactions. Frequent check on the weight, blood pressure, pulse, complete blood counts, sedimentation rates, urinalysis, blood urea and liver function tests were made.

RESULTS:

There is, perhaps, no other entity as difficult to evaluate as the treatment of headache. It is obvious that many factors enter into treatment of each case, and the actual treatment must be manifold. Our overall approach and treatment of each problem has been adequately outlined many times in the past.[27] It is against such a background that the effect of orphenadrine citrate has been evaluated. All of the techniques utilized before in our patients are continued in this present series, the only exception being that orphenadrine citrate is used instead of the analgesics, sedatives or tranquilizing drugs that the patient had formerly taken. Each patient has been instructed to begin therapy with one tablet, 100 mg. two times daily as the maintenance dose. Any patient who has received satisfactory results for acute attacks with other medication, such as sedation or ergotamine compounds, has been instructed to continue its use as required. We have found that once the patient finds an agent that will control the attack, he receives such reassurance that this serves to remove what we call the "fear complex," of being overwhelmed by a severe attack.

Table I presents the analysis and results of all patients treated in each type of headache.

Results of treatment were based upon the improvement reported after institution of orphenadrine citrate therapy. As described above, at times this was the only medication or therapy; at other times it was added to other treatment. As can be seen, most patients had been under treatment for a considerable period of time before the new drug was prescribed. They therefore had established a baseline record of frequency and severity of headache attacks. In this manner, they were

TABLE I

RESULTS OF TREATMENT WITH ORPHENADRINE CITRATE

	Vascular	Tension	Arthritis	Post-Traumatic
Total Number of Patients	44	44	23	14
Males	8 (22%)	11 (25%)	7 (30%)	8 (57%)
Age Range of Males Treated	23-72	27-68	40-79	32-73
Females	36 (78%)	33 (75%)	16 (70%)	6 (43%)
Age Range of Females Treated	21-75	18-86	30-83	27-53
Duration of Symptoms Before Beginning Treatment with Orphenadrine Citrate:				
1-30 days	1 (2%)	2 (5%)	0 (0%)	2 (14%)
1-6 months	3 (8%)	4 (9%)	3 (13%)	4 (29%)
6 months or longer	40 (90%)	38 (86%)	20 (87%)	8 (57%)
Duration of Treatment with Orphenadrine Citrate:				
5 to 30 days	19 (43%)	9 (21%)	4 (18%)	4 (28%)
1 to 6 months	14 (32%)	11 (25%)	5 (21%)	3 (22%)
6 months or longer	11 (25%)	24 (54%)	14 (61%)	7 (50%)
RESULTS OF TREATMENT:				
Excellent	4 (9%)	15 (34%)	7 (30%)	6 (43%)
Good	9 (21%)	22 (50%)	12 (52%)	6 (43%)
Poor	31 (70%)	7 (16%)	4 (18%)	3 (21%)

able to determine the effect of orphenadrine citrate. Response was recorded as excellent if the severity and frequency of headache was reduced at least 75 per cent. It was recorded as good if the frequency and severity was reduced 50 to 75 per cent, and poor if less than 50 per cent improvement was recorded.

VASCULAR HEADACHE:

The 44 patients with vascular headache included eight males (22%), ranging in age from 23 to 72 years, and thirty-six females (78%), ranging in age from 21 to 75 years. One patient (2%) had symptoms for three weeks before beginning medication. Three patients (8%) had symptoms for one to six months before therapy, and forty patients (90%) had symptoms longer than six months. Nineteen patients (43%) continued treatment for one month or less, fourteen patients (32%) for one to six months, and eleven patients (25%) for longer than six months. Excellent results were reported by four patients (9%). Good results were reported by nine patients (21%) and poor results by thirty-one patients (70%). These figures indicate that orphenadrine citrate is not usually effective in primary vascular headache.

TENSION HEADACHE:

The forty-four patients in this group included eleven males (25%), ranging in age from 27 to 68 years, and thirty-three females (75%), ranging in age from 18 to 86 years. Two patients (5%) had symptoms for less than one month before therapy, four patients (9%) for less than six months, and thirty-eight (86%) for longer than six months. Nine cases (21%) continued therapy for one month or less, eleven (25%) for one to six months, and twenty-four (54%) for longer than six months. Excellent results were reported by fifteen patients (34%), good results by twenty-two patients (50%) and poor results by seven (16%).

ARTHRITIS:

Of the twenty-three patients with definite cervical arthritis and/or discogenic disease, seven (30%) were males, ranging in age from 40 to 79 years, and sixteen (70%) were females, ranging in age from 30 to 83 years. No patients had symptoms for less than one month before therapy, three patients (13%) for less than six months and twenty (87%) for longer than six months. Four patients (18%) continued therapy for one month or less, five (21%) for one to six months,

and fourteen (61%) for longer than six months. Excellent results were reported by seven patients (30%), good results by twelve patients (52%) and poor results by four (18%).

POST-TRAUMATIC:

Of the fourteen patients with a definite history of head injury preceding onset or flareup of symptoms, eight (57%) were males, ranging in age from 32 to 73 years, and six were females (43%), ranging in age from 27 to 53 years. Two patients (14%), had symptoms for less than one month before therapy, four patients (29%) for less than six months, and eight (57%) for longer than six months. Four patients (28%) continued therapy for one month or less, three (22%) for one to six months, and seven (50%) for longer than six months. Excellent results were reported by six patients (43%), good results by five patients (36%) and poor results by three (21%).

TOXICITY

Each of the 220 cases reported had a complete medical and laboratory evaluation before and at the end of this study. Those patients who continued to take the drug for more than two months had repeated laboratory studies performed at regular intervals. These studies included recording of blood pressure, pulse, weight, complete blood count, sedimentation rate, blood thymol and transanimase determinations, urea, uric acid and urinalysis. The reason for this intensive laboratory study is the frequency with which blood dyscrasias, liver or kidney damage has occurred with many of the newer chemical compounds. Analysis of our results showed no **incidence of any toxicity.**

SIDE EFFECTS

Every attempt was made to record all side effects noted, as recorded in Table II.

TABLE II

SIDE EFFECTS

	Present	Continued to Tolerate Drug at Same Dosage	Subsidence of Side Effects with Lower Dosage	Discontinued Medication Because of Side Effects
Gastrointestinal Upset	7		4	3
Dizzy, Confused or Swimming Sensation of the Head	6	2	4	
Increased Excitement, Nervousness or Restlessness	6		4	2
Sleepy or Dopey Sensation	4	1	3	
Feeling of "Big Head" or Increase in Headache	3	1	2	
Bad Taste or Dryness of the Mouth	2	2		
Skin Rash	1		1	
Burning Sensation of the Face and Vagina	1		1	
Blurred Vision	1			1
Constipation	1	1		

Analysis of Table II should have further explanation. While thirty-two incidences of side effects were recorded in the 220 cases, they were reported by only seventeen patients. Two patients reported three different reactions, six patients reported two different reactions and fourteen a single reaction. Most side effects were minimal and easily controlled, as seen by the fact that seven patients continued to take the same dose without further mention of the symptoms. Nineteen controlled reactions by lowering the dose. Only six patients elected to discontinue the medication because of side effects.

Gastrointestinal upset, dizziness, confusion or swimming sensation in the head, excitation, nervousness and restlessness, sleepiness, increase in headache or sensation of a "big head," were the most frequent reactions reported.

OTHER CONDITIONS TREATED

During the seventeen months of this headache study, we had the opportunity to treat 95 additional patients with orphenadrine citrate. Many of these patients had specific elements of muscle spasm as an indication for treatment, whereas others (injuries and arthritides) had little or no objective muscle spasm present. Orphenadrine citrate was prescribed, along with other accepted methods of treatment. Cases treated and results are recorded in Table III.

TABLE III

OTHER CONDITIONS TREATED

Backache Without Neurologic Signs	33	23 (70%)	7 (21%)	3 (9%)
Arthritis: Cervical Arthritis or Bursitis of the Shoulder with Shoulder and Arm Pain	20	4 (20%)	11 (55%)	5 (25%)
Chest Wall Pain	10	5 (50%)	3 (30%)	2 (20%)
Arthritis: Dorsal or Lumbar Spine with Back and Hip Pain	6	1 (17%)	4 (66%)	1 (17%)
Acute Injury to the Lumbar Intervertebral Discs with Backache	5	0	1 (20%)	4 (80%)
Aches or Cramps in the Legs	5	0	3 (60%)	2 (40%)
Arthritis: Generalized	4	0	3 (75%)	1 (25%)
Paralysis Agitans (Parkinsonism)	3	0	1 (33%)	2 (67%)
Torticollis	3	1 (33%)	2 (67%)	0
Carcinoma	2	0	0	2 (100%)
Arthritis: Coccyx	2	0	2 (100%)	0
Knee Injury	1	0	0	1 (100%)

Analysis of these miscellaneous conditions, treated with orphenadrine citrate, indicates that those conditions associated with objective evidence of muscle spasm (backache, with or without arthritis, shoulder and arm pain with bursitis, chest wall pain and torticollis) reported over 75 per cent good or excellent results. Our patients with carcinoma, paralysis agitans, acute lumbar disc discogenic disease, generalized arthritis, leg cramps and joint injuries reported predominantly poor results.

DISCUSSION

Orphenadrine citrate has proved to be a useful adjunct in the treatment of any type of head or neck pain in which skeletal muscle spasm is a factor. The drug acts on the higher levels of the central nervous system, interfering with reflex pathways for pain and skeletal muscle contraction. Thus orphenadrine relaxes skeletal muscle in spasm but does not reduce the general tonus of skeletal muscles.

Simple postural or humidity changes, fatigue, or exposure to drafts, often produce **physical** muscle spasm at the back of the head and neck leading to a muscle tension headache. Emotional factors leading to generalized increased anxiety and tension are often accompanied by muscle contraction in the same area. Primary vascular headache is often accompanied by heightened tension on the emotional level or can produce muscle tension about the head and neck on a simple reflex basis. Structural changes of the cervical spine are likewise commonly accompanied by abnormal muscle contractions. Accident involving the head and neck cause sudden stretching, tearing, swelling and

(Continued on Page Eighteen)

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Muscle Relaxation

(Continued From Page Sixteen)

displacement of ligaments, muscular, vascular and nerve elements about the head and neck. Apprehension, worry and fear following head injury naturally results in further spasm of the tissues involved. **Orphenadrine citrate exerts a specific action in those situations where muscle spasm is present.**

SUMMARY AND CONCLUSIONS

1. One hundred and twenty-five patients with headache or neck pain were treated with orphenadrine citrate for a period ranging from five days to seventeen months.

2. The prime indication for its use was muscular spasm.

3. Of the forty-four cases with primary vascular headache, four (9%) reported excellent results, nine (21%) good results, and thirty-one (70%) poor results. Vascular headache is therefore not usually an indication for orphenadrine therapy.

4. Of the forty-four cases of primary tension headache, fifteen (34%) reported excellent results, twenty-two (50%) good results, and seven (16%) poor results.

5. Of the twenty-three cases with arthritis of the cervical spine, seven (30%) reported excellent results, twelve (52%) good, and four (18%) poor results.

6. Of the fourteen cases of post-traumatic headache syndrome, six (43%) reported excellent results, five (36%) good, and three (21%) poor results.

7. Of the ninety-five cases with pain other than headache, those entities with primary muscle spasm reported at least 75 per cent good and excellent results. These included backache, bursitis of the shoulder, chest wall pain and torticollis.

8. Results were predominantly poor in paralysis agitans, generalized carcinoma, acute lumbar intervertebral disc injury, generalized arthritis, leg cramps and joint injuries.

9. Seventeen of 220 patients reported thirty-two separate incidences of side effects. Two patients had three different reactions. Six patients had two different reactions and fourteen patients reported one reaction. Continuation of therapy, or reduction of dosage satisfactorily controlled these reactions in most instances. Six patients elected to discontinue therapy because of reactions.

10. Complete physical and laboratory examinations revealed no incidence of toxicity to the drug.

11. **Management of the patient as a whole following a thorough diagnostic evaluation is the keystone of therapy for any type of headache. The specific muscle relaxing action of orphenadrine citrate provides a welcome addition to the general management of the headache patient.**

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Some Important Features of Migraine

By

WALTER C. ALVAREZ, M.D.
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AFTER having read most of the literature on migraine, I cannot remember having seen an article in which the fact was stressed that many persons who have inherited a tendency to the disease have a very mild form of it. Usually it is so mild that when the patient goes to see a doctor, he or she does not think to mention the occasional scotoma or the occasional mild headache or brief spell of dizziness or nausea or abdominal distress. Only when migraine is unusually severe, does it become a curse.

As everyone knows, the mildest forms are seen in men. That these mild forms are unknown to most physicians, who do not think to ask about them, will become obvious to anyone who will ask and find, that hundreds of his patients have experienced a few scotomas, and in their youth, perhaps, had a few sick headaches. The fact that some of the old writers say that at least half of their **men** patients had severe headaches with vomiting shows clearly that they were failing to recognize the hundreds of mild cases. I must be seeing 10 or 20 men with scotomas to one who has a sick headache.

Once, I made a test study of this at a cocktail party at an A.M.A. meeting. There, I quickly found 44 men who said that, occasionally, they had a scotoma, but only six of these men ever had had a headache following the scotoma, and in most cases, their headache had been mild. All of the six men with sick headaches had, as I expected, an extra inheritance of a tendency to psychosis, which apparently was what had made their migrainous syndrome severe. My study of hundreds of cases of very severe migraine, and especially migraine that persisted past middle age, showed usually a second inheritance from some psychotic, alcoholic, very eccentric, or epileptic forebears.

To show how mild migraine commonly is, I need only mention the way it has come down through my family. My mother was decidedly migrainous, but she didn't have sick headaches. She would have times when she was so sensitive to light and sound that she would have to spend a day in a darkened room. My older son, now 50, has had only two scotomas in his life; my younger son has had a few, and a daughter has had a few. These three persons do not have headaches. In the last 15 years, I have had a scotoma every few weeks, but never in my life have I had a headache after a scotoma. I have a granddaughter who has had a few spells of what looked like mild cyclic vomiting — the migraine of young girls.

If a physician is ever going to help hundreds of slightly migrainous women, he will have to learn to recognize as probably migrainous the trimly built, well-dressed, attractive, and well-educated little woman who walks quickly into his office, and then answers his questions quickly and to the point. It will be well if he suspects that she is migrainous, because only if he does this will he understand right away why she is complaining of a number of nervous symptoms. She is not likely to tell him about her occasional scotoma or about the sick headaches that she had when she was in her teens and which disappeared in her twenties.

On studying a few hundred migrainous women, I found the typical build and appearance in 74 per cent, and I found the typical temperament in 95 per cent. These people are perfectionists who want everything done just so and on time and as planned. They are highly subject to fatigue and when they get tired, they **suddenly** become **very** tired.

There are certain tell-tale phases about a migrainous attack which I rarely see emphasized in the literature. One is that the headache can be bilateral and it often runs back to the nape of the neck. Another is that often, with a headache, a woman feels cold all over and frightened, as if she were all alone in the world. It is highly significant that, in a typical migrainous spell, the woman is unwilling or unable to eat. Also, it is important to note that aspirin usually has no effect on a sick headache. Men can sometimes get sufficient relief with a tablet of empirin compound with half a grain of codeine, if they take it quickly.

It is important to teach one's assistants that they will find many a history of headache confusing until they ask and learn that the woman has at least two types of headaches—one a mild, ordinary "nervous" one, and the other a terrible "sick" one. I always suspect migraine when I hear that a headache wakes the person out of sleep or comes after a certain stimulus, such as a fright, or some excitement, like that of seeing a dog run over in the street, or after having light come into the eyes in a slanting direction, perhaps from a window, or after looking at an "eye-twisting" wallpaper or dress pattern.

I am sure that there isn't enough in the literature on the fact that many migrainous women suffer from pain in the right upper quadrant of the abdomen. I didn't know how frequent this was until a few years ago, when I went over the records of a few hundred migrainous women. This study showed me also that a considerable percentage of migrainous women suffer from spells of abdominal pain of a gastric crisis type.

As we all know, many of these women, because of their pain, have their gallbladder removed. So far, I have never seen anyone **permanently** relieved of migraine by the removal of even a stone-containing gallbladder. I never realized until I went over the records of hundreds of migrainous women how often they get operated on uselessly. Many have a hysterectomy performed by a surgeon who thinks that the removal of a uterine myoma will help the headaches, or who feels sure that an artificial menopause will cure them. I have never seen a case in which the removal of a myoma cured migraine, and in the last 110 consecutive cases I have studied in which a surgeon induced a menopause with the hope of curing migraine, he failed in every case.

I do not believe that migraine and epilepsy have much in common. These two diseases appear in two very different types of person. Also, the electroencephalograms of migrainous women are normal unless there is epilepsy in the family; also, in my experience, anti-convulsive drugs do not help migrainous persons unless the electroencephalograms are dysrhythmic.

Some women who have severe migraine in middle age or late in their life are mildly psychotic because of a poor nervous inheritance. The storminess of their emotions seems to keep the migrainous attacks coming.

A point that I would emphasize is that patients are wrong when they think that a complete and thorough examination will lead to the cure of a severe migraine. One diagnoses migraine from a good history and never from a complete examination. The trouble always comes from one place in the body and this is the brain. There is probably an irritable spot in or near the visual center.

One can, I think, be sure that headaches are migrainous if one finds that they disappear after a pregnancy, after an attack of jaundice, after a bad accident with perhaps a broken hip, or after a big operation or a severe attack of fever.

Few writers have emphasized the fact that headaches often constitute the least part of a migrainous woman's troubles. I will never forget the woman who first taught me this. She said angrily, "I wish you would quit talking about my headaches; I can stand them. What I want to be cured of is my sickliness, my nervousness, my tendency to great fatigue, my inability to keep up with my husband, and go with him to a football game, and especially I want to be able to keep appointments when I make them."

No physician is likely to give much help to a migrainous woman unless he spends considerable time questioning her to find out what her life problems are. Often he can help her most by teaching her how to avoid some of the strains she has to meet. Often, a husband could almost cure his migrainous wife by being kinder, more considerate, and more understanding, and perhaps by giving up some annoying habit that greatly distresses the woman.

Some physicians think that migraine is all food allergy, but I am sure that allergy is only one factor. Many of the migrainous women I see know enough to avoid one or two foods, the eating of which will bring a sick headache, but still they have trouble because there are 20 or 30 ways in which the woman can bring on a spell. An interesting point which I cannot now remember having seen discussed is that, in some cases, a severe food allergy will not bring on a headache. To illustrate: I am tremendously sensitive to chocolate and chicken fat, but these two substances never produce in me even a scotoma, and certainly never a sick headache. One causes in me canker sores and the other causes a violent gastrointestinal upset. This peculiar action of allergens on migrainous persons deserves some study.

SUMMARY

The author points out a number of little-known facts about migraine, such as: 1) it occurs most commonly in forms so mild that the person never mentions them to his physician; 2) these very mild forms are usually found in men; 3) men commonly have scotomas, but these are rarely followed by a headache; 4) a physician should learn to recognize the typical migrainous woman in a minute, because only then may he know why she has many nervous complaints; 5) it is important to note that in a typical spell a woman cannot or will not eat; 6) aspirin has no effect; 7) it helps to know that an atypical headache is tirggered by a typically migrainous stimulus; 8) many migrainous women suffer from abnominal pain; 9) migraine and epilepsy are not related; 10) severe and late-lasting migraine is often produced by two inheritances, one of migraine, and one of psychosis or epilepsy; 11) it helps in the diagnosis to know that a woman's headaches disappeared during a pregnancy or after a bad accident or a bad fever, or especially after an attack of jaundice; 12) food allergy is only one cause for migrainous spells. Also, a migrainous person who is highly sensitive even to chocolate, may never get a headache after eating this food.

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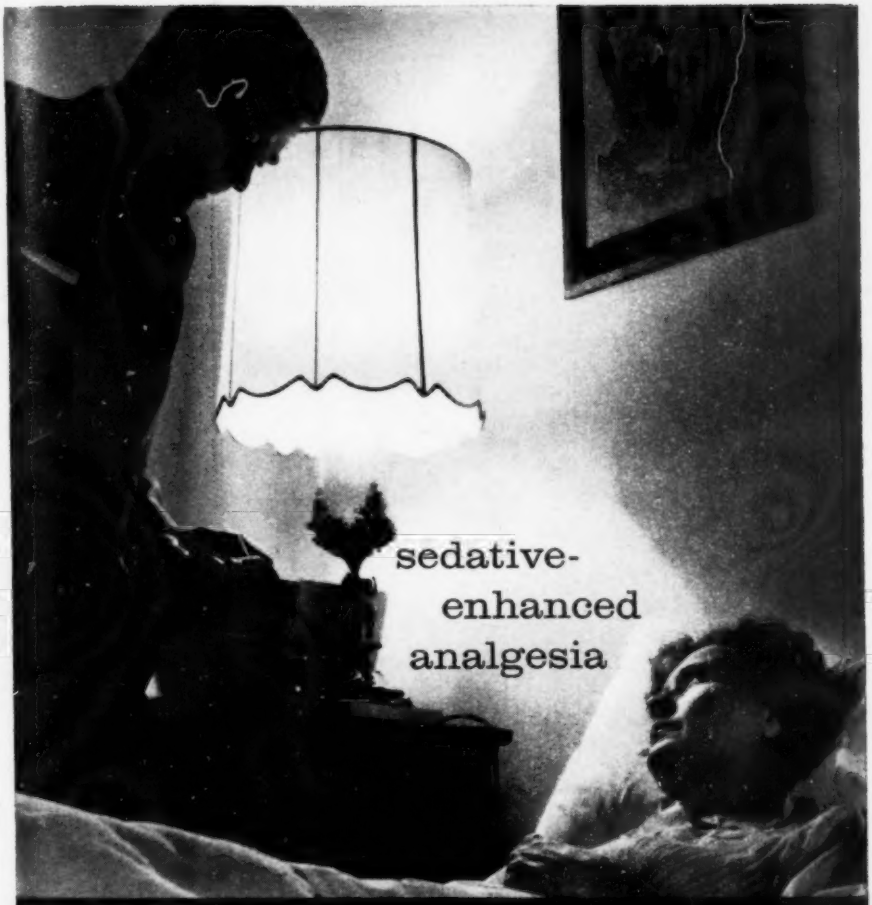

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Pain In The Anterior Portion Of The Temples

HENRY D. OGDEN, M.D.
NEW ORLEANS, LA.

THE differentiation of various types of vascular headache may be quite difficult. The intracranial variety may be due to dilatation of the cerebral arteries, including those at the base of the brain. The arteries of the pia and the dura may play a part. However, the location of pain that is due to dilatation of the vessels on the outside of the head may pose a diagnostic problem. Pains that are due to occipital artery dilatation or those due to the middle meningeal may be easily recognized. The frontal artery type of pain has been described.[1]

The belief that pain in vascular headache is due entirely to pain originating from the external carotid arteries and not at all from the internal carotid vessels has been stated to be fallacious. It is logical to assume that if the pain arises from one arterial system that it may also arise from another arterial system; provided, that both systems affect the head. A more complete description of frontal headache has been outlined.[1-2]

It has been stated that pain which originates from dilatation of the branches of the ophthalmic artery which is a branch of the internal carotid artery affects principally the frontal area.[1]

The syndrome migraine is caused by dilatation of extracranial vessels, mainly the superficial temporal arteries. The superficial temporal is the main vessel involved in migraine, and the pain is generally regarded to be hemicranial. It later may involve the other side or even become generalized. While the differentiation of pain into the frontal type may be regarded by some as being arbitrary, it is felt by the author that the syndrome of frontal pain is quite distinct and should be differentiated from the general concept of typical migraine.

It has been also shown[1] that pain of the frontal variety is of the truly vascular type, for reasons given below.

It is obvious that the frontal type of headache possesses at times some of the characteristics of migraine, or the symtamotology that has become identified with vascular headaches. These include prodomal symptoms such as aurae, visual difficulties, nausea and even vomiting, throbbing type of headache, et cetera. Also, in a recent study, it was found that the ergotamine drugs were effective in an impressive percentage of cases of frontal headache. The ergotamine drugs are known to be exceptionally helpful as vasoconstrictors of cranial vessels. While some may feel that the response seen in individuals with frontal headache is due to nasal decongestion, the author feels that it is due to the direct constricting effect of the ergotamines on arterial musculature.

Our main point is that temporal pain arising from the superficial temporal artery must be distinguished from pain arising from other vessels. While the differentiation may be academic in reality, since the main point to remember is that we are dealing with the vascular type of head pain, it seems to be necessary to

reassure the purists. Pain arising from the superficial temporal originates in a branch of the external carotid artery—while pain originating from a branch of the ophthalmic artery in reality has its origin in a branch of the internal carotid artery.

I,[1] and others have all too often designated pain in the temples as being the "migraine" variety. However, it should be borne in mind that the superficial temporal artery really is in the posterior portion of the temple. There are many cases of pain in the region of the temple which are not in the posterior area. Moreover these cases of pain often "dovetail" in with the description of frontal headache.[1]

Why this discreptancy? It is purely anatomical.

Pain in the anterior portion of the temple often fits in with the frontal type of head pain, which has been described. In fact, pain in this area is often accompanied or associated with pain in the frontal area. It is also often seen with nasal symptoms such as blockage. This nasal edema may be slight and barely perceptible to the patient.[3] However, if the patient is questioned very carefully he may tell us that there is some slight degree of nasal stuffiness either before or during attacks of headache. Some patients will state that relief of pain is accompanied by an increased nasal discharge. In fact, the use of nose drops will help many individuals since the preparation is usually a vasoconstrictor. However, the routine use of vasoconstrictor solutions topically in the nose is to be

ILLUSTRATION NO. 1

condemned, because all too often they result in the "rebound" mechanism. In other words, the nasal mucosa becomes dependent on the topical vasoconstrictor.

However, the point in this discussion is why pain in the anterior portion of the temple should so often accompany the frontal type of headache. It seems to the author that the lacrimal artery is the main vessel involved. First of all, it should be remembered that the anatomical distribution of pain must depend on the arterial distribution. Let us first quote Gray's anatomy:

"The Lacrimal Artery (a. lacrimalis) arises close to the optic foramen, not infrequently before it enters the orbit, and is one of the largest branches derived from the ophthalmic. It accompanies the lacrimal nerve along the upper border of the Rectus lateralis, and supplies the lacrimal gland. Its terminal branches, escaping from the gland, are distributed to the eyelids and conjunctiva: of those supplying the eyelids, two are of considerable size and are named the lateral palpebral arteries; they run medialward in the supper and lower lids, respectively, and anastomose with the medial palpebral arteries, forming an arterial circle in this situation. The lacrimal artery gives off one or two zygomatic branches, one of which passes through the zygomaticotemporal foramen, to reach the temporal fossa, and anastomoses with the deep temporal arteries; another appears on the cheek through the zygomatico-facial foramen, and anastomoses with the transverse facial. A recurrent branch passes back-

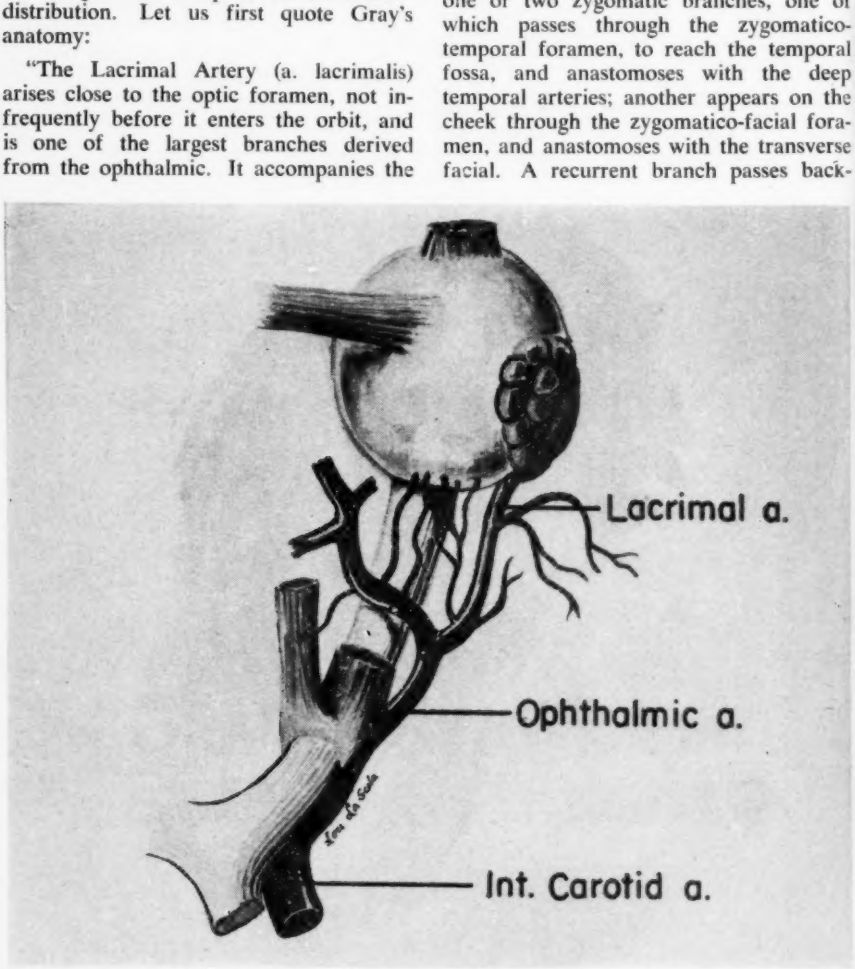

ILLUSTRATION NO. 2

ward through the lateral part of the superior orbital fissure to the dura mater, and anastomoses with a branch of the middle meningeal artery. The lacrimal artery is sometimes derived from one of the anterior branches of the middle meningeal artery."

Then let us quote Cunningham:

"The lacrimal artery arises from the ophthalmic on the lateral side of the optic nerve. It runs forward with the lacrimal nerve, along the upper border of the lateral rectus, to the upper lacteral corner of the orbit, where it gives off branches to the lacrimal gland. In its course it gives off muscular branches to the lateral and superior recti, and twigs which accompany the zygomatico-temporal and zygomatico-facial branches of the zygomatic nerve to the temporal fossa and the face, respectively. The lacrimal artery gives off also anterior ciliary arteries to the eyeball, and it ends in the lateral palpebral arteries which supply the conjunctiva and the eyelids.

The muscular branches are arranged in two sets; one supplies the upper and lateral orbital muscles, the other the lower and medial muscles. They anastomose with muscular branches from the lacrimal and the supra-orbital arteries, and they give off anterior ciliary arteries.

The anterior ciliary arteries arise from muscular branches of the ophthalmic and from the lacrimal artery. They pierce the sclera behind the corneo-scleral junction and join the greater arterial circle of the iris. They give off small episcleral ar-

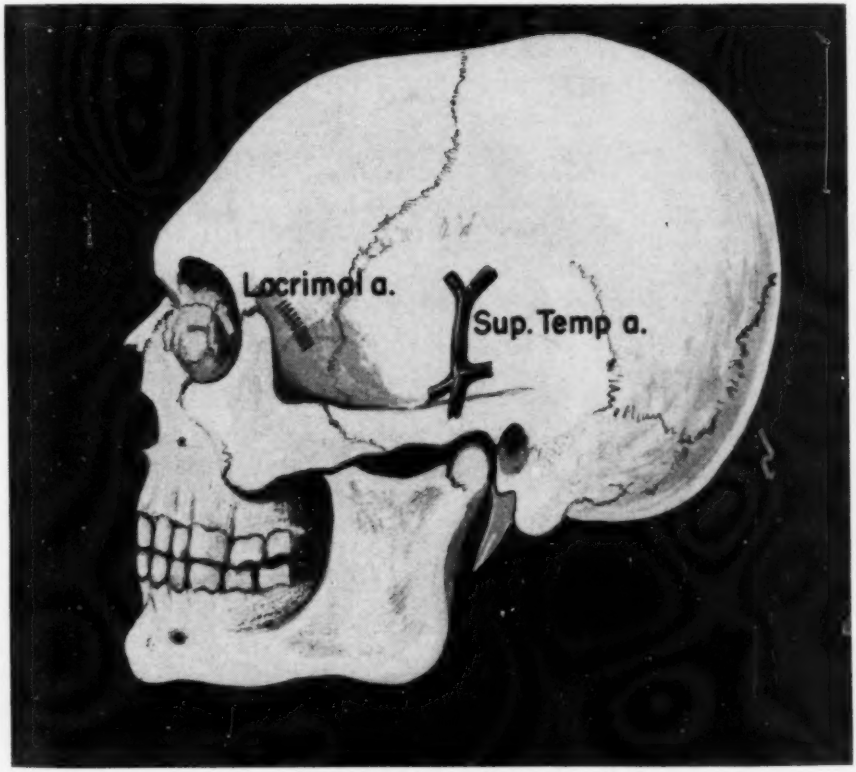

ILLUSTRATION NO. 3

teries, which pass forward on the surface of the sclera to the corneo-scleral junction and give off in turn minute anterior conjunctival arteries, which loop back in the conjunctiva to anastomose with posterior conjunctival branches of the palpebral arteries."

Then in Illustration No. 3 we see the difference in areas supplied by the superficial temporal artery as compared with the lacrimal artery.

After a consultation with Dr. Goss, the professor of anatomy at the Louisiana State University School of Medicine, it was found that the lacrimal artery is not prominent in many individuals, therefore it is inconstantly present. However, it apparently may cause head pain in quite a number of patients.

In these occasional cases in whom the lacrimal artery is given off by the middle meningeal, the vessel enters the orbit through the superior orbital fissure.

CONCLUSIONS:

Dilatation of the lacrimal artery apparently is the cause of many cases of headache. This fact has not been recognized by many headache workers.

American Association for the

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ANNUAL MEETING

PARK SHERATON HOTEL

JUNE 25, 1961

NEW YORK

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1:00 P.M.-5:00 P.M.

THE ROLE OF PLACEBO RESPONSE IN CLINICAL HEADACHE EVALUATIONS

GUNTHER H. FREY, M.D.
Monmouth Junction, N.J.

HEADACHE is of such common occurrence that it might understandably be called humanity's "inevitable" symptom. Among those who seek a physician's care, headache has been estimated to be the chief complaint in more than half of the patients.[1] And among the general population, the incidence may be higher, judging from the reported presence of recurrent headache in over 60 per cent of persons surveyed in a large-scale statistical study.[2]

Just as headache is a particularly frequent form of the pain-discomfort manifestation, so is it also a major clinical target of symptomatic pharmacotherapy. There is quite obviously no scarcity of drugs that are offered, in a number of categories, for use in the relief of headache. Recent years have witnessed many introductions of new medications for this purpose.

In the midst of this pharmaceutical abundance which still grows at an accelerated pace, the most widely used drugs in current treatment of headache remain the long-established non-narcotic analgesics. These drugs, sometimes described as the "antipyretic" or "salicylate-order" analgesics, are typified by aspirin (acetylsalicylic acid) and phenacetin (acetophenetidin).

Analgesics of this type—which, to repeat, are the mainstay of headache treatment in general both as to frequency of use and total amount consumed — have been a special concern of the present author during some years. Among the various aspects of analgesic research that one might pursue, two interrelated areas hold exceptional interest and importance; these are the methodology of clinical drug evaluations, and the role played by the placebo effect.

In presenting this report, which covers extensive clinical studies in headache analgesia conducted with drugs of salicylate order, it seems proper to set forth briefly certain underlying principles that governed the approach.

For one thing, the author believes that use of the placebo is extremely important, even essential in evaluating the therapeutic worth of new drugs in situations, such as headache, where there is only the subjective response of the patient to guide interpretation. In fact, one may go further and consider that placebo alone is not sufficiently revealing and that the new drug should be subjected to trials involving both a placebo and a well-established, standard (or bench-mark) medication with the same mode of action and therapeutic effect of similar order. This view was adopted for the studies reported in this paper.

Another principle that obtained was that of adequate patient population. In the author's opinion, it is necessary to set a minimum limit of about 100 patients per compound in such (mild, orally administered) drug evaluation as these—in order to obtain a statistically meaningful baseline for the placebo comparison. As an aside, it may be stated that this is both feasible and resembles clinical reality fairly well. However, in two active drug comparisons, the differences obtained may be so slight that statistical validity would require sometimes a trial group of several thousand patients per series. Such a procedure would not be practical; nor would it resemble everyday clinical practice.

Returning to the placebo-controlled approach, it is important to mention that the author adopted the double-blind principle of drug administrations. This mode of investigation, widely accepted as the optimal way to deal with subjective responses, is well suited to the placebo-reference drug — "unknown" drug approach. It should also be mentioned that two methods of evaluation seemed to be most meaningful—the first by comparison of placebo and drug performances in different patients; the second by comparative responses in the same patients acting as their own controls. Both the "comparative" and "cross-over" methods were used in these investigations, which were conducted in three separate phases.

Methods and Materials

The first phase of study entailed eight series of dose-administrations (placebo and active drugs) in a total group of 2,554 patients. Each dose represents a separate, single episode of headache (classified as "tension headache" in the great majority of instances). Since treatment, or rather dose-administration, was provided as patients presented themselves, it took about six weeks to complete each of the eight series, or one year to conduct the entire first phase.

All of these patients belonged to a "closed" institutional population; they were all males, ranging from 16 to 65 years in age, and they were approximately equally divided in number of Whites and Negroes.

The doses administered were all standardized at two tablets of identical physical appearance.

The six materials used in this phase of study were: (1) placebo, (2) acetylsalicylic acid, (3) sodium salicylate, (4) aspirin-phenacetin-caffeine combination, (5) combination of aspirin and APAP (n-acetyl-paraminophenol), and (6) combination of aspirin-caffeine-salicylamide and APAP. Acetylsalicylic acid, which served as a standard reference drug, was given in standard 10 grain therapeutic dosage (5 gr. per tablet) and the other active medications were administered in amounts conventionally accepted as analgesic equivalents.

As each patient presented himself at the dispensary for treatment of his headache episode, he was given a two-tablet dose of a coded material in randomized fashion. He then remained in the waiting room, being permitted to read, converse, or play checkers. At the end of 60 minutes, a nurse made sure that the patient had recorded results (as "complete relief," "partial relief," or "no relief"). This supervised and prompt recording was deemed necessary to offset the frailty of human memory, which is a significant factor in subjective responses especially among relatively unsophisticated individuals.

The second phase of investigation was conducted over a three-month period in a group of private out-patients seen at a headache clinic. These 150 selected patients were considered representative of chronic headache sufferers among the population at large. There were 98 females and 52 males; the ages ranged from 15 to 67, with the mean at 38.4 years. All of the patients were white; more than half of them (83) were housewives, with the others in various occupational categories.

In this phase, the patients were given (in randomized fashion, under double-blind coding) three dose-administrations of each of three materials in the course of nine different headache episodes occurring during the three-month period. The materials used were (1) placebo, (2) acetylsalicylic acid, and (3) aspirin-phenacetin-caffeine combination.

Since all these patients were unusually well-trained observers (because of chronicity and considerable prior experience with drugs and drug-evaluations), this second phase of study permitted some additional observations. Thus, headache episodes were recorded as to cause and as to location (frontal, occipital), and the patients were entrusted with the recording

(Continued on Page Thirty-Four)

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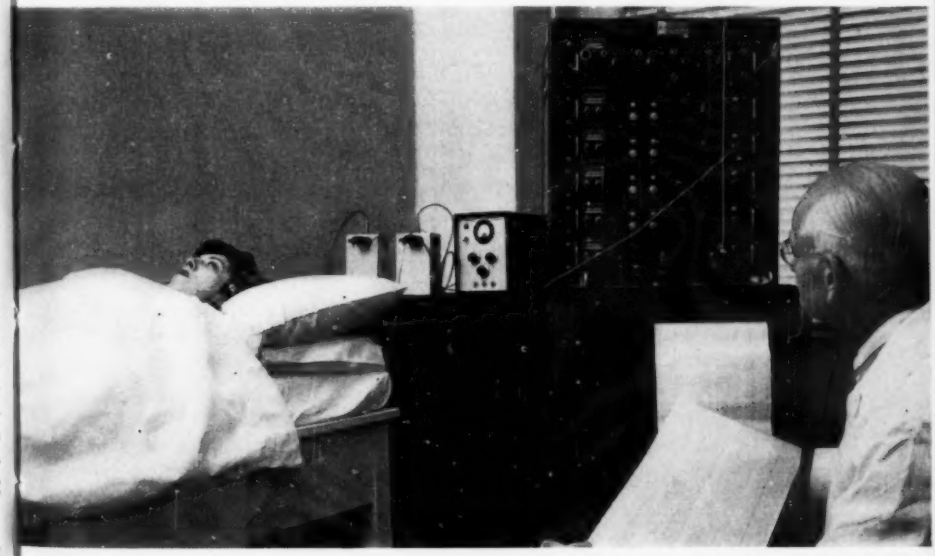

Placebo Response

(Continued From Page Thirty-Two)

of results both as to complete, partial or no relief, and as to the time required for complete relief when this result occurred. For all practical purposes, the patients in Phase 3 may be considered as representing the general population in the same way as the patients in Phase 2.

In this third phase, each patient coming in for treatment was given—on three different occasions of headache episode—three different dose-administrations of only a single material, the placebo. In short, this phase constitutes an evaluation of placebo vs. placebo vs. placebo response. It is worth stressing that this procedure was carried out in every respect (double-blind, randomized) according to the previous patterns which the clinic patients associated with active drug therapy.

Results

Table 1 shows the therapeutic results recorded in the eight comparative series of the first phase. These data have been subjected to biostatistical analysis and the relevant factors concerning statistical significance are shown in Table 2.

Although Table 1 lists percentages for partial relief (PR), the author feels that these figures are too relative and indefinable for meaningful evaluation of drug response. It seems by far preferable to base interpretations of results on the nearest thing to absolute data available in subjective studies—that is, the percentages for complete relief (CR), and for no relief (NR). Another consideration to be borne in mind is that each of the eight series represents a separate sub-study. Since the patients are different in each series, and since the results also vary—especially with respect to the placebo response—it is not valid to make numerical comparisons or summations of one series with another.

The data concerning the second phase of this study are shown in Tables 3, 4, 5 and 6. These are in the main, self-explanatory; two comments are offered on Table 4. First, it is pointed out that the randomized administration of doses produced an unusually close correlation of percentages. Second, it may be interesting to note that the headache survey previously mentioned[2] reported an incidence of 72.7 per cent for frontal headache and of 15.6 per cent for occipital location. These close correspondences give further support to the representative status of the patient population of this phase.

Tables 7 and 8 give the data for the third phase—the "all-placebo" phase of the study. These tables show that this phase of investigation involved not only the same type of headache patients as in the previous phase using active drugs, but also pretty much the same distribution of causes of headaches and similar patterns of placebo response with respect to both complete relief and no relief. It would appear that this third phase is the only investigation of its kind—that is, a series in which placebo response is evaluated three times in the same subjects—a placebo vs. placebo vs. placebo response evaluation.

Discussion and Conclusions

Although these investigations were conducted in three different phases, certain points may be taken up as relating to the subject as a whole. It is the author's opinion that placebo response, particularly when coupled with use of a standard reference drug, has in this study (as in many others) shown itself an excellent guide in determining, "the bedrock of therapeutic expectancy" in a given analgesic for a given purpose. It appears justifiable to state that the placebo-reference drug approach, using the double-blind technique with either comparative or cross-over controls, is an excellent way to obtain meaningful data in evaluating subjective therapeutic responses.

However, in stressing the important role of the placebo in aiding the evaluation of analgesics, the author does not intend to give any impression that this role of the placebo continues on into the routine of prescribing drugs in practice. In fact, once a drug has been evaluated,

it must be understood that statistically significant differences between placebo and an active drug are clinically meaningful even when the arithmetic difference seems numerically small. A placebo is essential in evaluating a new drug; but it is not a placebo but active drugs that one prescribes in clinical practice. Therefore, one should not mentally be subtracting placebo responses from active drug responses to measure probable clinical effectiveness; one should rather make a comparison with a standard reference drug with an established order of potency.

In Phase 3, it became apparent that among this group of 150 patients only 18, or 12 per cent, were shown to be definite and consistent placebo reactors as judged by the fact that they had reported complete relief resulting from each of the three administrations of placebo. Another 36 of these patients or 24 per cent were consistent non-reactors—that is, they did not obtain complete relief following any of the three placebo administrations.

Another point of interest is the finding (Phase 1) that these trials did not substantiate the familiar pharmacology textbook reference to so-called mutual potentiation of the mild, non-narcotic analgesics. This whole area of opinion is cloudy, and invites much more detailed research.

TABLE 1 — PHASE I

THERAPEUTIC RESPONSES IN 8 SERIES OF DRUG ADMINISTRATIONS — FIRST PHASE OF STUDY

Series	Drug	No. Pts.	% Complete Relief	% Partial Relief	% No Relief
I	Placebo	123	43	39	18
	Aspirin	106	46	36	18
	Aspirin-phenacetin-caffeine	127	50	31	19
II	Placebo	105	40	29	31
	Aspirin	104	51	35	14
	Aspirin-phenacetin-caffeine	110	55	27	18
III	Placebo	110	49	27	24
	Aspirin	102	59	25	16
	Aspirin-phenacetin-caffeine	103	70	19	11
IV	Placebo	102	47	34	19
	Aspirin	101	60	29	11
	Aspirin-phenacetin-caffeine	100	63	27	10
V	Placebo	109	43	37	20
	Aspirin-phenacetin-caffeine	106	57	29	14
	Aspirin-phenacetin-caffeine	106	51	37	12
VI	Placebo	100	48	38	14
	Aspirin	102	61	27	12
	Sodium salicylate	101	52	32	16
VII	Placebo	103	36	32	32
	Aspirin	100	48	42	10
	Aspirin, APAP*, caffeine and salicylamide	110	44	43	13
VIII	Placebo	110	40	29	31
	Aspirin, APAP*, caffeine and salicylamide	102	56	29	15
	Aspirin and APAP*	112	46	31	23

*APAP = n-acetylparaminophenol, acetoaminophen.
All percentages are given after rounding off decimals to the nearest integer.

Side effects played no significant part in any phase of these investigations.

On the other hand, sodium salicylate, which is reputedly too irritant for general oral use, did not cause any appreciable complaints of gastric irritation among the 101 patients who received this drug (Series 6, Phase 1).

In spite of the separation into three phases of study, the investigations conducted give a consistent total impression. Here again, further conclusions are left for the individual judgment of the reader.

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TABLE 2 — PHASE I

STATISTICAL ANALYSIS OF RESPONSES (FROM TABLE 1)
SIGNIFICANCE OF PLACEBO — DRUG DIFFERENCES

Series	Drug	Complete Relief t	Complete Relief p	No Relief t	No Relief p
I	Placebo-aspirin	0.45	[70%	0	—
	Placebo-aspirin-phenacetin-caffeine	1.1	[90%	0	—
II	Placebo-aspirin	1.62	95%	2.98	] 99%
	Placebo-aspirin-phenacetin-caffeine	2.2	] 98%	2.2	] 98%
III	Placebo-aspirin	1.46	92%	1.45	92%
	Placebo-aspirin-phenacetin-caffeine	3.2	] 99%	2.6	] 99%
IV	Placebo-aspirin	1.88	97%	1.6	95%
	Placebo-aspirin-phenacetin-caffeine	2.3	98%	1.8	97%
V	Placebo-aspirin-phenacetin-caffeine	2.06	98%	1.2	[90%
	Placebo-aspirin-phenacetin-caffeine	1.2	[90%	1.6	94%
VI	Placebo-aspirin	1.88	97%	0.4	[70%
	Placebo-sodium salicylate	0.6	[70%	0.4	[50%
VII	Placebo-aspirin	1.74	96%	2.18	] 98%
	Placebo-aspirin-APAP*-caffeine salicylamide	1.2	[90%	3.4	] 99%
VIII	Placebo-aspirin-APAP*-caffeine salicylamide	2.35	] 99%	2.81	] 99%
	Placebo-aspirin and APAP*	0.9	[90%	1.4	91%

t = Students t test.
p = Probability factor.
*APAP = p-acetylparaminophenol, acetoaminophen.

TABLE 3 — PHASE II

CAUSES OF HEADACHE EPISODES IN 150 SELECTED PATIENTS
(SECOND PHASE OF STUDY)

	Tension	Common Cold	Sinusitis	Pre-menstrual Tension	Eye-strain	Other	Total
Number of episodes	641	229	163	105	131	81	1350
Percentage*	47%	17%	12%	8%	10%	6%	100%

*Percentages have been rounded off to the nearest integer.

TABLE 4 — PHASE II

LOCATION OF HEADACHE CORRELATED WITH DRUG ADMINISTRATIONS, IN 150 SELECTED PATIENTS (SECOND PHASE OF STUDY)

	Total Episodes	Placebo Administrations	Aspirin Administrations	Aspirin-Phenacetin-Caffeine Administrations
Frontal	979 = 72%	319 = 79%	337 = 75%	323 = 72%
Occipital	177 = 13%	57 = 13%	58 = 13%	62 = 14%
Other	194 = 15%	74 = 17%	55 = 12%	65 = 14%
	1350 = 100%	450 = 100%	450 = 100%	450 = 100%

Percentages have been rounded off to the nearest integer.

TABLE 5 — PHASE II

THERAPEUTIC RESULTS IN SECOND PHASE TRIALS, AVERAGED FOR 3 ADMINISTRATIONS OF EACH OF 3 DRUGS IN 150 PATIENTS

Drug	Complete Relief	Partial Relief	No Relief
Placebo	43%	31%	26%
Aspirin	58%	28%	14%
Aspirin-phenacetin-caffeine	57%	31%	12%
and			
Placebo-aspirin-phenacetin-caffeine	p =] 0.01		p = 0.01
Placebo-aspirin	t = 4.2		p =] 0.01

t = Students t test.

p = Probability factor.

Percentages have been rounded off to the nearest integer.

TABLE 6 — PHASE II

TIME REQUIRED FOR COMPLETE RELIEF IN SECOND PHASE TRIALS (CUMULATIVE PERCENTAGES)

	Minutes							
Drug	5	10	15	20	25	30	40	60
Placebo	1%	4%	18%	37%	51%	73%	81%	95%
Aspirin	1%	8%	20%	40%	55%	72%	80%	94%
Aspirin-phenacetin-caffeine	1%	8%	20%	38%	51%	76%	81%	92%

Percentages have been rounded off to nearest integer.

TABLE 7 — PHASE III

CAUSES OF HEADACHE EPISODES IN 150 SELECTED PATIENTS
(THIRD PHASE OF STUDY)

	Tension	Common Cold	Sinusitis	Premenstrual Tension	Eye-Strain	Total
Number of episodes	188	89	67	55	57	450
Percentages*	42%	20%	15%	12%	11%	100%

*Percentages rounded off to nearest integer.

TABLE 8 — PHASE III

THERAPEUTIC RESULTS IN THIRD PHASE TRIALS,
PLACEBO ADMINISTERED TO 150 PATIENTS IN 450 HEADACHE EPISODES

Drug	Complete Relief	Partial Relief	No Relief
Placebo (first episode)	39%	32%	29%
Placebo (second episode)	42%	26%	32%
Placebo (third episode)	44%	28%	28%

Percentages have been rounded off to nearest integer.

OFFICIAL PROGRAM

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Study of Headache

Park Sheraton Hotel, New York City

Sunday, June 25, 1961

9:10- 9:30 A.M.—"Modern Migraine Management," R. E. Ryan, M.D.

9:30- 9:50 A.M.—"Tic Douloureaux, A New Allergic Approach to the Etiology and Treatment," William J. Hanes, M.D.

9:50-10:10 A.M.—"Controlled Studies on 200 Patients With the Use of New Medication for Headaches," Henry D. Ogden, M.D.

10:10-10:20 A.M.—Coffee Break

10:20-10:40 A.M.—"Clinical Caprices of Histaminic Cephalalgia," L. L. Lovshin, M.D.

10:40-11:00 A.M.—"A Survey of 332 Cases of Headache in Private Practice of Otolaryngology," Joseph C. Elia, M.D.

11:00 A.M.-12 Noon—BUSINESS MEETING

2:00- 2:20 P.M.—"Control of Crop Headaches," Perry S. MacNeal, M.D.

2:20- 2:40 P.M.—"New Approaches in Treatment of Headache," Lester S. Blumenthal, M.D., and Marvin Fuchs, M.D.

2:40- 3:00 P.M.—"Headache in the Aged," Benj. O. Morrison, M.D.

3:00- 3:20 P.M.—"Headache in Childhood," John P. McGovern, M.D.

3:30- 4:30 P.M.—"INFORMAL QUESTION AND ANSWER PERIOD." Discussants to be chosen during the meeting.

EQUALS PARENTERAL INJECTION IN THERAPEUTIC RESPONSE

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Bibliography: 1. Blumenthal, L.S. and Fuchs, M., Am. J. Gasterol., *33*, 189-202, 1960. 2. Ryan, R.E., Med. Times, *88*, 6, 739-742, 1960. 3. Segal, M.S., J.A.M.A., *169*:1063-1071, 1959. Write Professional Service Department for literature and trial supply.

Wampole Laboratories, Stamford, Conn. 141WS

ABSTRACTS

Humoral Agent in Vascular Headache of Migraine Type

Chapman, L. F., Arch. Neurol., 3:223-318 (Sept.) 1960

Specimens of subsurface tissue fluid were collected from painful sites during headache and contrasted with specimens from nontender sites. "Headache" specimens contained abnormally large amounts of (1) neurokinin, a vasodilator polypeptide that has been observed in this laboratory to be formed during neuronal activity in man (axon reflex and antidromic vasodilation); and (2) a protease capable of forming neurokinin when incubated with plasma globulin. (This protease was found to be increased in cerebrospinal fluid during severe vascular headache also.) The amount of these substances present locally in the subsurface fluids paralleled closely the intensity of pain experienced. Vascular headache of the migraine type is the result of large artery dilation plus the local accumulation of neurokinin and nourokinin-forming enzyme, both implicated in local vasomotor control. The result is a painful, sterile, inflammatory reaction neurogenically induced.

Basilar Artery Migraine

Bickerstaff, E. R., Lancet—Vol. 1:15 (Jan. 7), 1961

It is probable that the migraine headache is due to excessive dilation of extracranial and dural vessels, and that in many patients this is preceded by construction of certain intracranial cerebral vessels resulting in transient ischemia and the production of the aura. Thus, constriction of ophthalmic or retinal vessels can produce unilateral loss of vision and various other eye symptoms; and, if the middle cerebral artery is involved, there are unilateral paresthesias of face, hand, and arm. Some prodromal symptoms cannot be explained in this way; they are not in the territory of the internal carotid, but of the basilar artery. The premonitory symptoms are different and reflect brainstem dysfunction. The author asked 300 patients with migraine to give an exact account of their prodromal symptoms. In this way 34 patients were discovered whose clinical symptoms suggested involvement of the basilar system. Symptoms consist in bilateral loss or disturbance of vision, ataxia, dysarthria, vertigo, tinnitus, and bilateral peripheral dysesthesias, followed by occipital headache. The syndrome is commonest in adolescent girls; this is shown in several case histories.

Bruxism and Chronic Headache

Berlin, R. and Dessner, L., Nord Med, Vol. 64 (Oct. 27), 1960

In describing bruxism, the authors point out that the hyperactivity of the muscles of mastication, involved in the grinding movements of the teeth that characterize this condition, may produce chronic headache. They present observations on 62 patients in whom headache was secondary to bruxism. The patients were treated with a specially designed "relaxation plate." A bite-plane is inserted between the upper and lower incisors, which results in raising the bite anteriorly, and makes impossible the habitual clenching of the jaws involved in bruxism. The use of such a plate cured the chronic headache in one or two months in 68% of the patients; 19% of the patients experienced great improvement, and 10% slight improvement. Only 3% derived no benefit. Some patients first served as their own controls in being treated with a plate that did not have the bite-raising effect. This plate proved ineffective. Six of seven patients later achieved a favorable effect, when the bite-raising incisor plate was substituted for the ineffective one.

Management of Glossopharyngeal Tic

Jones, Robert K., Pennsylvania J. J. 63:1113-1116, 1960

Intracranial section of the ninth nerve relieves glossopharyngeal neuralgia. Pain usually starts in the tonsillar fossa and extends to the ipsilateral ear but sometimes begins in the ear and spreads to the pharynx and base of the tongue or is restricted to the ear. Paroxysms of pain of increasing intensity last twenty to thirty seconds and are often followed by a burning sensation lasting two to three minutes. Tingling anterior to the ear and along the lower margin of the ipsilateral mandible may occur.

Patients may not be able to define the site and origin of pain or the region of spread. Discomfort may be precipitated by chewing, swallowing, or yawning. A sleeping patient may be awakened when salivary secretions pass over a trigger area in the posterior pharynx.

Glossopharyngeal neuralgia may be associated with cardiac arrest and syncope. Atropinization before an anticipated attack prevents cardiac and syncopal symptoms but not throat and ear pain. After the effects of atropine have worn off, the carotid sinuses are massaged with the head in different positions. Manipulation will usually precipitate syncope or cardiac arrhythmia if the patient has hyperirritable carotid sinus disease. No symptoms will occur if the patient has true glossopharyngeal neuralgia with vagal component, unless massaging the neck causes the patient to swallow and secretions flow over the trigger area. Anesthetizing the posterior wall of the pharynx may abort the attack, confirming the diagnosis. However, complete cocainization of the pharyngeal wall is difficult.

Causes of neuralgia of the ninth nerve include elongation of the styloid process, atheromatous plaques on the vertebral artery, tuberculous laryngitis, ossification of the stylohyoid ligament, and nasopharyngeal and intracranial tumors.

Intracranial section of the ninth nerve relieves pain and produces permanent unilateral anesthesia of the soft palate and pharyngeal wall from the eustachian tube to the epiglottis and the posterior third of the tongue, with loss of taste over this area. Salivary secretion, diminished in the immediate postoperative period, returns to normal within three months. Peripheral section is not recommended.

Otorhinolaryngological Considerations on the Temporal Arteritis Syndrome

Font, J. H., J.A.M.A., 174:853-856, Oct., 1960

Temporal arteritis is the name given to a local systemic symptom-complex that attacks persons in the later years of life. Prior to the development of the full-blown picture of temporal arteritis, the victims usually suffer, for various lengths of time, from a generalized, debilitating, subacute febrile disease such as a nasopharyngitis or an upper respiratory disease.

Inflammation of the temporal arteries of the scalp was observed in three patients. The temporal arteritis syndrome is a puzzling, distressing painful disease. The constantly shifting angitis gives this syndrome a protean nature characterized by successive exacerbations and remissions. Variability in the distribution of the vascular pathology plays a part in the causation of head and face symptoms that may simulate any number of otorhinolaryngological conditions. Temporal arteritis can be a protracte disease capable of irreparable damage. Proper treatment of the corticosteroids must begin immediately after it is suspected and must be continued throughout the course of the disease.

Migraine — A Deadly Disease

Ask-Ipmark. E., Brit. M. I., 823-825, 1960

Ophthalmoplegic migraine, more often than not due to an aneurysm of an artery of the circle of Willis, may involve the oculomotor nerve, so that a distension of the aneurysm will cause oculomotor palsy with ptosis and other symptoms. Rupture may be fatal.

Paroxysmal tachcardia of auricular origin is an equivalent to migraine and in an individual some attacks are typical migraine, others paroxysmal tachycardia. In attacks of paroxysmal tachycardia, there is always the possibility that the heart rate attained may be so rapid as to prevent the auricular contraction from ejecting the blood into the ventricules because of the almost simultaneous contraction of the ventricules. This "critical" heart rate is about 180. If no adequate assistance is given in such a case the circulation may be totally blocked.

There are rare instances of migraine with a heart rate of 20-40. If in such a case ergotamine tartrate is injected intravenously, cardiac standstill may easily be induced.

Another complication which has become increasingly common and is a very real danger, is renal; its anatomic character is interstitial nephritis, and it not uncommonly causes death from uremia. It is apt to be encountered in patients with migraine who have taken a large amount of phenacetin, or similar compounds, over a number of years. Small doses of this drug used only occasionally seem to be fairly safe.

If the intracranial aneurysms frequently responsible for migraine and occasional cases of paroxysmal tachycardia are excepted, the danger is obviously mainly iatrrgenic and lies in the use of ergotamine tartrate, and particularly of phenacetin preparations.

Ergotamine for Vascular Headache

Speed, Wm. G. III, Am. J. M. Sc. 240:327-331, 1960

Prompt relief is effected in many patients with vascular headache by oral inhalation of mucronized ergotamine tartrate. Alveolar - capillary absorption, achieved by means of a self-propelled aerosol device (Medihaler) delivering the drug in 0.36 mg. doses with each depression of the valve, gives adequate blood concentrations more consistently and rapidly than any other method, except subsutaneous or intravenous injection.

Among 65 patients, results of inhalation were excellent or good in 91.3% with migraine, 84.6% with histaminic cephalalgia, and 83.2% with tension headache. Usually two or three inhalations were required for complete relief.

Headache From Clenching or Grinding of Teeth

Monica, W. S., Ann. Otol. Rhin. & Laryng. 68:1159-1162, 1960

Grinding and clenching of the teeth causes sustained contractions of the masticatory muscles which may result in partial tetany and so produce headaches. Malocclusion or ill-fitting dentures may be the basis of these symptoms. The resulting hypertrophy of the masseter muscles leads to a chipmunk expression. A smooth acrylic splint, like a boxer's gumshield, which allows the mandible to move easily, will abolish the occlusal incongruities. Wearing such a splint at night cured two patients of persistent frontal headaches which they had had on waking for some years. The headaches and the tight feeling in the jaws, recurring if they left off the night splints, were again relieved if the splints were worn. Not all with malocclusion grind the teeth and not all patients who habitually grind their teeth have headaches, but this is an occasional cause of persistent frontal headache that can be readily relieved.

Pain Relief in Dysmenorrhea, Premenstrual Tension Headache and Postpartum Pain

Wainer, A. S., Clin. Med., 2331-2334, Nov. 1960

Phenyramidol was administered to 225 patients having pain associated with dysmenorrhea, premenstrual tension headache, and postpartum pain. Effective relief was obtained in the majority. In postpartum patients, results compared favorably with those obtained when codeine was given.

Phenyramidol, a pain-relieving drug offering analgesic and muscle-relaxing properties, was found to be effective in the management of dysmenorrhea and premenstrual tension. As an analgesic in postpartum pain a combination of phenyramidol and aspirin was successfully substituted for a codeine mixture, indicating phenyramidol to be an effective, convenient agent which is not limited by the precautions necessary when administering narcotics.

Ergotamine Tolerance Must Be Determined Individually

Cameron, E. A., and French, E. B., Brit. Med. J. 2:28, 1960

That ergotism can occur from accepted therapeutic doses of ergotamine in the absence of contraindications was demonstrated forcibly by a case in the Eastern General Hospital of Edinburgh. A woman was admitted because of intense pain in the legs and arms. Her face and neck were flushed, neither pulse nor blood pressure could be measured in the extremities, yet the carotid pulse was pounding. These factors, plus blueness and lack of reflexes, indicated intense arterial spasm. There was no history of vascular disease. Inquiry revealed that 1 mg. ergotamine tartrate tablets had been taken for menorrhagia. The day after starting this drug the patient became nauseated and her legs and feet were cold and blue. Within two days, the condition was further complicated by muscle cramps, paresthesia, fever, leukocytosis and proteinuria. All attempts to mitigate this vascular crisis with anticoagulants and vasodilators were ineffective. Five days after admission, the radial pulse and blood pressure were measurable and, when it was clear that maximum improvement had occurred, it was necessary to amputate both legs, right thumb and part of the index finger.

Migrainous Scotoma

Alvarex, W. C., Am. J. Ophth. 49:489-504, 1960

That many physicians are unacquainted with this phenomenon is clear from the reports of scores of patients who have been alarmed by their experience with it and unsuccessful in getting a diagnosis.

Study of records of the experiences of 618 migrainous persons, 53% of the men and 36% of the women having scotomas, and 12% of the men and 0.7% of the women having scotomas without headache, disclosed the following:

1. Men are more likely to see the zigzag line, women being more likely to have atypical scotomas.

2. Scotomas can appear before or with headache.

3. Many persons have their scotomas mainly late in life, winding up with their headaches and nausea gone and only scotomas left.

4. The whole brain is disturbed with a scotoma. There may be a slight scotoma. There may be a slight aphasia, with numbness, formication, pins and needles, muscle weakness, frequency of urination, or pain in the thorax or abdomen.

5. For hours after a scotoma there may be sensitiveness to light.

6. A spell of poor vision lasting 20 or 30 minutes is diagnostic of migraine. Scotomas due to epilepsy last only a few seconds and may be associated with visions of faces, these not occurring with pure migraine.

7. Electroencephalograms during scintillating scotoma usually show nothing abnormal.

8. Migrainous scotomas tend to change in character with age. Brilliant scotomas are seen in children.

Vascular Headaches: Transpulmonary Absorption of Ergotamine

Blumenthal, L. S., and Fuchs, M., M. Ann. District of Columbia, 30:10-12, 59, 1961

In a series of 41 women and 20 men, ranging in age from 16 to 72, the duration of headaches had been from one to sixty years. All had been observed for a minimum of six months and their responsiveness or lack of response to other forms of therapy had been evaluated. All were treated with ergotamine tartrate by inhalation; the device used (Medihaler) was calibrated to deliver 0.36 mg. of ergotamine tartrate per single inhalation. Of 42 patients with vascular headaches (migraine or histamine), 83% had satisfactory results; of 19 with nonvascular headaches (tension or post-traumatic), 37% had satisfactory results. The rate of onset of relief and the total dosage required are comparable to those achieved by intravenous administration of this agent.

Mandibular Joint Dysfunction: Diagnosis

Copland, J., Oral Surg., 13:1106, 1960

Outstanding symptoms present in 186 cases were pain and clicking. Pain was most frequently felt in the region of the mandibular joint itself, followed by the angle of the jaw and the ascending ramus. In every case in which pain was a symptom it could be elicited or increased in intensity by firm palpation over the affected joint while the mouth was opened. Clicking usually occurred at the end of the normal extent of opening, and again as the condyle passed back through this position in the closing movement. This is probably caused by the condyle passing over the anterior edge of the articular disc when the synchronous movements of the condyle and disc are disturbed. Painful clicking was particularly marked in cases of recurrent subluxation or forward dislocation. The most frequent eccentric mandibular movement found was deviation of the mandible on opening. This occurs when condylar movement is unequal; the jaw then deviates to the side where movement is more limited. Over half the patients had malocclusions, but these are not always considered responsible for joint dysfunction. In almost a third of the cases examined muscle tension was considered to be the primary etiologic factor. Muscle tension is most often manifested by teeth clenching and bruxism.

Combination Drug Therapy for Headaches: Evaluation by an Internist, Allergist, and Otorhinologist

Flohr, Leonard; Grater, Wm. C.; Baldwin, James:
Clin. Med. March, 471-474, 1961

Satisfactory relief of headache was obtained in 74 per cent of 132 patients. Sinutab was evaluated by the combined efforts of an internist, allergist, and otorhinologist. It was proven to be excellent symptomatic therapy for headaches, 98 of 132 patients (73%) reporting complete relief following treatment.

Best response was obtained in patients with headaches complicating allergic rhinitis (90%) and sinusitis (83%). Tension headaches were relieved in 62% of the cases, migraine in 54%.

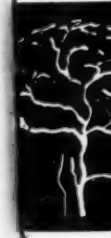
Studies in Headache

Dalessio, D. J., and others, Arch. Neurol—Vol. 4:235 (Mar.) 1961

UML-491, 1 methyl-D-lysergic acid butanolamide bimaleinate, is being investigated for its effectiveness in the prevention of vascular headache. Sterile inflammatory responses were produced in seven patients, using 1.0% manganese butyrate solution as an irritant, before, during, and after receiving UML-491 in therapeutic amounts. In addition, a young patient is described who developed major arterial insufficiency of the lower extremities while taking this medication. Results indicate that UML-491 possesses anti-inflammatory properties of a nonspecific nature, and secondarily induces arterial vasoconstriction, when given in therapeutic amounts. It is suggested that the vasoconstriction is dependent upon the capacity of UML-491 to increase the sensitivity of the individual to his own vasoconstrictive substances, and that the vasoconstriction, indirectly induced, is the basis of the therapeutic action which this agent possesses in the prevention of vascular headache.

Severe Arteriospasm After Use of Ergotamine Tartrate Suppositories

Young, Jess R., and Humphries, Alfred W., JAMA, 175:107-111
April 1, 1961

Every patient on ergot therapy for headaches should be carefully watched for toxic manifestations, and the pulses of the hands and feet should be periodically checked. At the first indication of toxicity, the administration of the drug should be stopped, and measures to produce vasodilation should be initiated. Vasodilating drugs may be tried. If the spasm is severe and the circulation of the limb is critical, sympathetic blocks and, if this is not sufficient, sympathectomy with periarterial stripping should be performed.

A 42-year-old woman had severe arteriospasm following the use of ergotamine tartrate suppositories for constant headaches of long standing. The patient completely recovered after bilateral sympathectomy, periarterial stripping, the administration of vasodilator drugs, and withdrawal of the ergot alkaloid.